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Oral contraceptive generations – Time to stop using a marketing myth to define nomenclature ☆,☆☆

Mitchell D. Creinin [a,*], Jeffrey T. Jensen [b]

[a] University of California, Davis, Sacramento, CA, USA
[b] Oregon Health & Science University, Portland, OR, USA

The use of the term "generation" to describe different formulations of combined oral contraceptives (COCs) has no basis in pharmacology and creates confusion when used to classify products in epidemiologic studies. Beginning in the 1990s, pharmaceutical company marketing teams introduced this nomenclature in an effort to boost sales of newer progestins. The idea of a "next generation" suggests improvement; that the newer ligands are safer or "better."

Prior to this time, clinicians had come to understand the concept of "high-dose" and "low-dose" oral contraceptive formulations based on the estrogen content. Unlike the term "generation," this demarcation was based on clinical outcomes and clear medical guidance; low-dose contraceptives, which contained ethinyl estradiol (EE) doses less than 50 mcg, had lower venous thromboembolism (VTE) rates than high-dose products [1].

In the early 1990s, the introduction of COC formulations containing newly patented progestins led to a marketing push that attempted to differentiate products using a generation concept.

- First generation: EE doses of 50 mcg or more, regardless of progestin;
- Second generation: EE doses less than 50 mcg combined with levonorgestrel (norgestrel) or norethindrone;
- Third generation: EE doses less than 50 mcg combined with desogestrel, gestodene, or norgestimate.

Pharmacologically, the available progestins in COCs at the time were derived from testosterone (19-nortesterone products), built on a fused phenantherene/cyclopentene 4-ring backbone common to all steroids. Although the term "gonane" in chemical nomenclature broadly refers to all compounds with this ring structure, in the contraception literature this term refers specifically to the 13-ethylgonanes, while the 13-methyl variants are commonly known as estranes. The gonanes include levonorgestrel (norgestrel), desogestrel, gestodene, and norgestimate.

The World Health Organization (WHO) recommends use of a drug classification system to provide a common language for describing the drug assortments in a country or region. This helps to identify problems in drug use, to initiate educational or other interventions and to monitor the outcomes of these interventions and compare data between countries [2]. The WHO recommends the Anatomical Therapeutic Chemical (ATC) classification system developed by Norwegian researchers. Logical systems classify drugs according to their mode of action, indications, or chemical structure. The generation nomenclature for COCs does not represent a logical pharmacologic classification system.

Consider that estrogen dose differentiates first and second generation products but not subsequent generations despite the introduction of pills with even lower EE doses and natural estrogens (estradiol and estetrol). While evidence does support a dose-dependent reduction in thrombosis risk associated with estrogen [3], the nomenclature implies, without evidence, a lowering of VTE risk with advancing generations [4].

Rather than continuing with a classification system based on estrogenicity, the generation scheme defines advancement beyond the second generation by progestin type only. The second generation combines an estrane (norethindrone) and a gonane (levonorgestrel) while the other gonanes are third generation. However, important differences exist between progestins based on numerous cellular, biological and clinical effects, confirming the lack of a class effect [5]. Accordingly, grouping these products together is false, inferring to providers, for example, that adverse effects within each grouping are the same.

Real life has demonstrated that differentiating progestins by generations is not the correct way to understand COCs. The marketing of norgestimate as a "third generation" progestin, provides a great example. Norgestimate is a pro-drug with the primary

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* Corresponding author.
E-mail address: mdcreinin@ucdavis.edu (M.D. Creinin).

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metabolites being a levonorgestrel derivative (levonorgestrel-3-oxime, renamed by the original company as norelgestromin) and levonorgestrel. Pharmacologically, it makes sense to classify norgestimate with levonorgestrel (as a second generation product) but pharmaceutical companies found a marketing benefit using the next, or "third generation" nomenclature.

The idea that new products represented a third (newer) generation implied everything would be "better," including safety. However, by the mid-1990s, epidemiologic evidence began to accumulate suggesting that the "third generation" pills incurred slightly higher risk of VTE than "second generation" pills [6,7]. While observational bias (healthy user effect, preferential prescribing) likely explains the increased VTE risk, these findings contradict the concept of increased safety with advancing generations. The same companies that spent a lot of money pushing "next generation" pills as "better" found themselves in the position of convincing clinicians they were really the same, resulting in confusion. We know now that progestin type has little impact on VTE risk induced by the potent synthetic estrogen EE used in most combined products [8–10].

The subsequent introduction of contraceptives containing drospirenone (a spirolactone) led to a new classification as "fourth generation" products by marketers and epidemiologists. However, even newer pills containing estradiol combined with dienogest (a novel non-ethinylated estrane) and nomegestrol acetate (a 19-norprogesterone) have not been referred to as "fifth generation." The inclusion of the natural estrogen pills with EE products as "fourth generation" provides further confirmation of the limitations of this nomenclature. Current evidence suggests equal or lower rates of VTE with estradiol pills compared to second and third-generation EE–containing products [11]. With the future holding the potential for a new COC with estetrol and drospirenone [12], categorization of combined hormonal products by generations will make even less sense.

The use of generations to define COCs was a marketing idea that has confused clinicians and the scientific community for years. This system does not provide valid differentiation of product safety or efficacy and was never intended to do so. Moreover, this non-evidence-based approach to describing COCs can result in a misunderstanding of the safety of progestin-only products. For example, one U.S. insurance company restricts coverage of a new progestin-only oral contraceptive containing drospirenone, with approval dependent on multiple criteria, one of which is: "Prescriber attests the benefits of drospirenone-containing, progestin-only contraceptives outweigh the potential risk of venous thromboembolism" [13].

As we move into the next decade, we recommend abandoning use of generations in publications and educational materials. Instead, use clear descriptive classifications that make biological and pharmacologic sense. We can better understand differences and potential benefits if we simply know what hormones are in the products we prescribe. We further advise that clinicians understand and refer to the various progestins according to established scientific nomenclature (e.g. estranes, gonanes, spirolactones, etc.) and evaluate individual products according to the results of clinical trials.

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